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Natural History Study of Pseudoachondroplasia

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Pseudoachondroplasia (PSACH) is a well-characterized autosomal dominant dwarfing condition. A great deal of information is available about orthopedic complications, but little is known about extraskeletal complications in adulthood. This study was undertaken to delineate the natural history of PSACH at all ages. Seventy-nine individuals responded to an extensive questionnaire that included information about deformities, operations, general health, chronic diseases, and reproduction. PSACH individuals were ascertained through the University of Texas Medical Genetics patient population, a genetic linkage study, and the social organization, Little People of America. The results show that PSACH individuals with a family history do not have a distinct or more severe phenotype than new mutation cases. There were no differences in the number of orthopedic complications, operations, or number of offspring between these two groups. Less than half of affected adults reported having total hip replacement surgery, which was less common than previously reported. Extraskeletal complications were generally uncommon. There were four cases of cancers in 41 individuals queried. Premature osteoarthritis was the major health problem for PSACH individuals. PSACH individuals are generally healthy but have problems associated with debilitating osteoarthritis.

KEY WORDS: pseudoachondroplasia, dwarfism, short stature, natural history

INTRODUCTION

Pseudoachondroplasia (PSACH) is an autosomal dominant dwarfing condition affecting the spine and long bones of the body. Although rare, it creates a significant burden on affected individuals and their families. Pseudoachondroplasia is not obvious at birth as both the birthweight and length are within the normal range. The initial indications are short stature and disproportionately short limbs, usually appearing between the age of 2 and 4 years [Maroteaux and Lamy, 1959]. Diagnosis depends on radiographical criteria. Skeletal changes vary between individuals and change over time. Radiographical findings include epiphyseal and metaphyseal abnormalities, anterior "tonguing" of the vertebrae, platyspondyly, and odontoid hypoplasia. Scoliosis, kyphosis, or lumbar lordosis and positional anomalies of the lower limbs such as genu varum or genu valgum are common. Typically, the latter deformities emerge after they have begun walking [Kopits, 1976; Wynne-Davies, 1986].

The natural history of pseudoachondroplasia, especially during adulthood, is not well characterized. Other skeletal dysplasias are associated with abnormalities involving organ systems outside of the skeletal system. For instance, individuals with achondroplasia can have neurological complications secondary to compression of the cervical and lumbar spinal cord [Butler and Hecht, 1990]. The primary aim of this study is to delineate further the natural history of PSACH at all ages.

MATERIALS AND METHODS

We studied 79 patients in which the diagnosis of PSACH had been made by a medical geneticist and/or a radiologist specializing in skeletal dysplasias. A previous PSACH natural history study, conducted in 1990 by the LPA, included 35 affected individuals. This study sampled those individuals and 32 affected individuals from 11 families and 12 isolated PSACH cases who were ascertained in the Genetics Clinic of the University of Texas Medical School at Houston, the Shriner's Hospital for Crippled Children—Houston Unit, Johns Hopkins Medical School, and the support organization, Little People of America (LPA). The control population for this study was composed of 32 unaffected relatives (23 unaffected sibs and 9 unaffected parents).

The questionnaire was based on the instrument used in the original 1990 study. Those questions were framed in an open-ended format that was not amenable to statistical analysis. The questionnaire was reformat-

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ted for the current study, converting the previous questions to a closed format with yes/no and age-of-onset outcomes. An additional set of closed questions regarding chronic conditions in later life was added.

The original data (n = 35) were transcribed confidentially into the new questionnaire. This was done because the previous participants did not wish to be recontacted. No effort was made to locate those individuals or their unaffected relatives to serve as controls. The number of responses, in some instances, varied between individuals because the information was not asked in the original questionnaire. The responses to the original survey were open-ended and written by the participants and, in some cases, questions were ignored or not answered. In situations where a respondent answered yes for a particular condition, it was followed by an age-of-onset question. Some participants could not provide this information, thereby decreasing the number of responses.

The second group of PSACH individuals (n = 44) was contacted by phone, and the goals and methods of the study were explained and informed consent was obtained. In the event that an affected individual was a minor, their parent or guardian was contacted and information was obtained from them. If an affected individual was deceased and a first-degree relative was available, this information was included in the study. Medical records were obtained whenever possible. The data were analyzed for the entire group (n = 79) and for the interviewed group (n = 44) to ensure reliability of responses.

The data collected was entered into a D-Base file and transferred into SPSS for statistical analysis [SPSS, Chicago, IL]. Both descriptive analysis and hypothesis testing using Chi-Square, Mann-Whitney, and Student's t-test were performed. Since the sample was small, the median values were reported instead of the mean values for continuous variables such as age-of-onset questions. Statistical significance was defined as $P < 0.05$.

RESULTS

Demography

Seventy-nine individuals were included in this study. Of 77 participants for whom the information was available, 33 (42.9%) were male and 44 (57.1%) were female. With the exception of one Haitian male, the entire population was Caucasian. Thirty individuals (38.0%) reported a family history and 40 (54.4%) represented new mutations in their families. This information was not available in six cases (7.6%), either because of adoption or lack of response in the original data.

Family History

To determine whether new mutation cases of PSACH were more severely affected than the inherited cases, family history status was compared to several variables—orthopedic complications (e.g., bowed legs, scoliosis, joint hypermobility), corrective operations, rate of Cesarean sections, and number of offspring.

Family history versus isolated cases were compared by the number of orthopedic complications. Orthopedic complications were divided into two groups separated by the median. Family history of PSACH was not a significant factor (n = 79, $P = .951$; n = 44, $P = .975$), suggesting there were no significant differences between familial and isolated cases in terms of orthopedic complications.

The relationship between family history and the number of operations was compared after grouping the number of operations into less than or equal to the median and greater than the median (2.0). Individuals with a family history of PSACH had significantly fewer operations than new mutation individuals ($P = .006$); however, when the interviewed group (n = 44) was compared, there was no significant difference in the number of skeletal operations ($P = .106$), suggesting that the interviewed group may have provided more reliable responses. The latter result indicates that there is no difference in the number of operations between new and familial cases.

There was no significant difference in the number of offspring or the percentage of Cesarean deliveries between familial and new mutation cases ($P = .176$ and $P = .375$, respectively).

Body Measurements

The median birth length of PSACH individuals (n = 47) was calculated to be 50 cm (range 42.5–55 cm). The median birth weight (n = 64) was 3.2 kg (range 0.86–4.5 kg). The median weight of mature individuals (n = 49) was 43.2 kg (range 25–68.2 kg). When grouped by gender, the median weight of women was 41.6 kg and 50 kg for men. The median height of affected adults (>17 years of age, n = 53) was 117.5 cm (range 90–147.5 cm). The median height of women was 116.3 cm and 120 cm for men. This finding agrees with the range described by Wynne-Davies et al. [1986] and Horton et al. [1982].

Skeletal Complications

The skeletal complications include: bowed legs, knock knees, "windswept" deformity, cervical spine instability, scoliosis, kyphosis, and lumbar lordosis. The proportions of individuals exhibiting these complications are shown in Table I. Bowing of legs was most common, reported by 83.8% of PSACH individuals.

A scale of severity was created based on the number of reported skeletal complications. The median value was 3.0 with a range of 1.0–7.0 (n = 44). Only four individuals reported more than four skeletal complications. The original written responses were excluded because of the incomplete information. Mature height was divided into two groups (mild short stature and severe short stature) separated by the medians for each gender. No significant difference was found when

TABLE I. PSACH Skeletal Complications

Skeletal complication	Frequency	Percent
Bowed legs	61/73	83.8
Scoliosis	34/70	48.6
Lumbar lordosis	31/67	46.3
Windswept deformity	11/67	16.4
Cervical spine instability	11/67	16.4
Knock knees	10/69	14.5
Kyphosis	4/66	6.1

TABLE II. Corrective Operations by Specific Skeletal Complications

Skeletal complication	Frequency of operation	Percent
Windswept deformity	8/11	72.7
Knock knees	7/10	70.0
Bowed legs	42/61	68.9
Scoliosis	8/33	24.2
Cervical spine instability	2/10	20.0
Kyphosis	0/4	0.0

stature was compared with orthopedic involvement, indicating there is no relationship between the two height groups and the proportion of orthopedic complications (n = 44, P = .961).

Skeletal Operations

The proportions of individuals reporting a specific orthopedic complication that required operations and the median ages at the time of surgery are presented in Tables II and III. Approximately three-fourths of individuals with a skeletal complication affecting the lower limbs (bowlegs, knock knees, windswept deformity) went on to have operations. The median number of reported operations was two (range 0–12).

The most common surgical intervention was the correction of bowleg deformities (68.9%; 42/61). Repeated operations were reported by 9 of 42 individuals undergoing a primary correction. Repeated or multiple surgeries do not appear to be as common as previously suggested [Kopits, 1976].

Seventeen of 51 (33.3%) affected individuals >19 years of age reported total hip replacement. The median age of this operation was 33.9 years and is consistent with reports suggesting that the typical age for total hip replacement is in the midthirties [Horton and Hecht, 1993].

General Health Problems

The frequencies of extraskeletal medical problems in PSACH were compared with controls and are shown in Table IV. They can be divided into six major categories: dental, visual, auditory, respiratory, cardiac, and neurological problems. Significant differences between the two groups were found with PSACH individuals having fewer sinus infections ($P < .001$), cavities ($P < .0001$), speech problems (P = .006), and allergies (P = .003). However, these results should be cautiously interpreted because of the small size of the control population.

TABLE III. Median Ages of Individuals at Operation

Operation	Number responses	Median age[a] (years)	Range[a] (years)
Bowed legs	39	8.0	2.0–27.0
Knock knees	10	12.0	6.0–33.0
Windswept deformity	7	11.0	6.0–34.0
Cervical spine instability	3	14.0	5.0–34.0
Scoliosis	6	13.5	11.0–24.0
Kyphosis	0	+	+

[a] + = no surgeries reported.

TABLE IV. Extraskeletal Medical Problems

Type	P value*	Number PSACH	Number control
Dental cavities	.000^	32/69	28/32
Dental overbite	.483	11/70	8/32
Dental braces	.814	12/71	6/32
Myopia	.948	32/72	14/32
Retinal tears	.134	0/71	1/32
Hearing problems	.636	9/72	4/32
Hearing evaluation	.138	32/57	24/32
Recurrent ear infections[a]	.577	16/72	5/32
Speech problems	.006	2/69	6/32
Speech therapy	.121	2/69	3/32
Sinus infection	.000+	13/72	17/32
Recurrent sinus infections[a]	.062	6/70	7/32
Allergy	.003	27/72	18/32
Chronic infection	.238	8/71	1/32
Pneumonia	.908	14/71	6/32
Bronchitis	.830	18/69	9/32
Hearing problems	.100	6/71	2/32
Mitral valve prolapse	.087	1/70	0/32
Neurological problems	.099	22/71	4/32
Seizures	.328	3/60	0/32
Sleep apnea	.579	2/69	2/32

[a] Recurrent = three or more episodes within 1-year period.
* Chi-square test of independence; ^ $P < .0001$; + $P < .0003$.

Neurologic complications were reported by 27.8% of respondents. The most common complication was numbness or tingling of the limbs. Sleep apnea did not occur more commonly in the PSACH group. Scoliosis was independent of neurological complications in both affected groups (n = 79, P = .584; n = 44, P = .564).

Chronic Conditions in Later Life

The presence of several chronic conditions in those 18 years of age or older was examined and included coronary artery disease, diabetes, emphysema, stroke, cancer, and arthritis. The PSACH population did not report emphysema, stroke, or diabetes. There was one case (2.4%; n = 41) of coronary artery disease reported in an individual who was 60 years old at the time of diagnosis. The number of responses in each category was too small for accurate statistical testing.

Of 41 responses, there were four (9.7%) instances of cancer, including uterine, ovarian, breast, and bladder cancer. The bladder cancer occurred in a 74-year-old man. The age of diagnosis for the cancers in women was 54, 49, and 51 years, respectively. Statistical testing was not performed; however, the localization of these neoplasias is cause for concern. Three of four were female-specific cancers. Only the individual with breast cancer did not survive the cancer.

Thirty-eight of 79 (48.1%) PSACH individuals had a clinical diagnosis of arthritis made by a physician; 22 (27.8%) did not have a diagnosis of arthritis and 19 (24.1%) did not answer the question. The distribution of arthritic pain in specific joints is listed in Table V with hip and knee arthritis occurring in just over 50% of

TABLE V. Distribution of Arthritic Pain by Region in PSACH

Affected joint	Frequency	Percent
Hip	34/64	53.1
Knee	31/60	51.7
Shoulder	21/58	36.2
Ankle	16/60	26.7
Neck	14/57	24.6
Elbow	13/58	22.4
Wrist	12/58	20.7
Hand	12/58	20.7
Foot	06/58	10.3

PSACH individuals. Median ages of arthritis onset are shown in Table VI. Arthritis affecting the hip, foot, and knee occurred at the median ages of 22.5, 16.5, and 19.0 years, respectively.

The distribution of arthritis was compared between the entire PSACH and control study populations (Table VII). In the PSACH population, there was a significantly higher rate of arthritis in the elbow ($P = .049$), hips ($P = .0007$), and knees ($P = .00006$, Mann-Whitney test). The weight-bearing joints are the primary sites for degenerative changes. Arthritis in the elbows has not been previously demonstrated.

The ages of onset for arthritis in the PSACH population were compared to the control group and are shown in Table VIII. PSACH individuals had a significantly earlier age of onset for arthritis in the shoulder ($P = .003$, median = 30.0 yr), hip ($P = .007$, median = 22.5 yr), knee ($P = .009$, median = 16.5 yr), and ankle ($P = .045$, median = 25.0 yr). However, the number of controls was small.

Reproduction

Reproductive status was determined in individuals >17.0 years of age (n = 40). The median number of offspring for PSACH individuals was 2.0 (mean = 1.48; range 0–8). There was no deviation from the expected Mendelian ratio of 50% affected offspring. When the affected and control populations were compared, the number of children born to affected individuals was significantly lower ($P = .042$; Mann-Whitney test).

The number of Cesarean section deliveries was recorded as a percentage of the total number of children born to each woman. Only three of 16 multiparous women reported never having a Cesarean delivery. The remainder had Cesarean deliveries for at least ½ of their deliveries. There was a significantly higher rate of Cesarean sections in the PSACH group than controls ($P < .001$; Mann-Whitney test). Cesarean deliveries have historically been recommended in women with chondrodysplasias because of the small size of the pelvis [Horton and Hecht, 1993].

TABLE VI. Onset of Arthritis by Joint in PSACH

Affected joint	Responses	Median age (years)
Knee	24	16.5
Foot	7	19.0
Hip	26	22.5
Ankle	15	25.0
Neck	12	29.5
Shoulder	19	30.0
Hand	10	32.0
Elbow	11	33.0
Wrist	11	34.0

TABLE VII. Comparison of Joint Arthritis in PSACH and Control Populations

Site	PSACH frequency	Control frequency	P value*
Neck	14/57	3/32	.151
Shoulder	21/58	6/32	.153
Elbow	13/58	2/32	.049
Wrist	12/58	4/32	.454
Hand	12/58	4/32	.328
Hip	34/64	5/32	.000†
Knee	31/60	3/32	.000†
Ankle	16/60	3/32	.094
Foot	6/58	3/32	.557

* Chi-square test of independence; † $P < .0001$.

Social Status

The responses to questions regarding level of education, marriage, and occupation were adjusted to include only those individuals >17.0 years. The median number of years of education was 14.0 (n = 42, range = 6.0–18.0). One-third of respondents held professional occupations, and most were employed.

Of the 44 responses regarding marital status, 15 (34.1%) were single, 22 (50%) were married, four (9.1%) were divorced, one (2.3%) had a significant other, and two (4.5%) were widowed. Within the group of married individuals (n = 22), 13 (61.9%) had spouses who were also short-statured.

DISCUSSION

Seventy-nine individuals with PSACH and 32 unaffected relatives responded to a survey regarding general health complications, chronic conditions, and skeletal features of the condition. There was no significant difference in severity between familial and isolated cases in terms of orthopedic involvement and reproductive capacity. Premature osteoarthritis begins in the lower limbs in late adolescence to early adulthood and then progresses to include the shoulders, elbows, ankles, and feet at a significantly earlier age than in unaffected individuals. There was no significantly increased frequency of extraskeletal medical problems commonly seen in other skeletal dysplasias. In some instances, the rate of these problems was significantly decreased compared with controls. An increased risk for chronic conditions such as heart disease or cancer was not demonstrated. In terms of reproduction, there were significantly fewer children born to PSACH individuals and significantly more Cesarean deliveries in PSACH women.

Follow-up studies regarding survival rates and causes of death in PSACH would be beneficial. In the present study, there were three deceased individuals whose causes of death were breast cancer, a heart con-

TABLE VIII. Comparison of PSACH and Control Age of Arthritis Responses

Affected joint	PSACH median age (yr)	PSACH number	Control median age (yr)	Control number	Mann-Whitney
Neck	29.5	12	55	3	.096
Shoulder	30.0	19	55	5	.003
Elbow	33.0	11	56	2	.029
Wrist	34.0	11	45	4	.296
Hand	32.0	10	56	4	.077
Hip	22.5	26	55	5	.007
Knee	16.5	24	57	3	.009
Ankle	25.0	15	56	4	.045
Feet	19.0	7	57	3	.053

dition, and a motor vehicle accident. Overall, individuals with PSACH are generally healthy but have significant morbidity associated with osteoarthritis.

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